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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
FORD, VANESSA L

ART UNIT	PAPER NUMBER
1645	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/545,772	WILKINS ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 3 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☒ Applicant's reply has overcome the following rejection(s): *Rejection of claim 14 under 35 U.S.C. 112, second paragraph*.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attachment*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *none*.

   Claim(s) objected to: *none*.

   Claim(s) rejected: *1,3,6,13-15,19,20,23-26,28-31,33,36-39,62 and 63*.

   Claim(s) withdrawn from consideration: *64-66*.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Advisory Action Attachment

1. Applicants amendment filed October 21, 2002 is acknowledged. Claims 1, 14 and 64-66 have been amended. Claims 2, 4-5 and 7-8 are cancelled. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 64-66 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

Rejection Withdrawn

3. In view of Applicant's amendment the rejection of claim 14 under 35 U.S.C. 112, second paragraph is withdrawn.

Rejections Maintained

4. The rejection of claims 1, 3, 6, 13-15, 19-20, 25-26, 28-29, 36-39, 62 and 63 under 35 U.S.C. 102 (e) as being anticipated by Thomas Jr. et al is maintained for the reasons set forth on pages 4-6, paragraph 5 of the previous Office Action.

The rejection was on the grounds that Thomas, Jr. et al disclose a composition that contains an antigen, a toxin (*Clostridium difficile, C. novyi, C. sordellii, C. perfringens, C. tetani and C. botulinum*) or a fragment or derivative thereof having adjuvant activity in a pharmaceutically acceptable vehicle (i.e. water, a saline solution, phosphate-buffered saline, a bicarbonate solution or a form of a suppository). Thomas, Jr. et al disclose that toxins included in the composition included *C. difficile* toxin A, *C.*

Difficile toxin B, both *C. difficile* toxins A and B, or a fragment or derivative thereof. Thomas, Jr. et al disclose that the *C. difficile* toxins contain the repeats which make up the carbohydrate binding domain of toxin A (ARU) or derivatives thereof. Thomas, Jr. et al disclose that the toxins may be recombinant, synthetic or part of a fusion protein which includes a *Helicobactor pylori* urease or polypeptide which facilitates purification of the fusion protein covalently conjugated to an antigen, chemically cross-linked to an antigen or toxoided (i.e. rendered less toxic) (column 3). Thomas, Jr. et al disclose that intranasal administration of antigens give rise to mucosal immune responses in the upper respiratory tract, gastrointestinal and genito-urinary tracts (column 4).

Since the Office does not have the facilities for examining and comparing applicant's immunogenic composition comprising *Clostridium difficile* toxin proteins with the immunogenic composition comprising *Clostridium difficile* toxin proteins of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the immunogenic composition of the prior art does not possess the same material structural and functional characteristics of the claimed immunogenic composition). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant urges that the immunogen to which an immune response is to be elicited is a polysaccharide component. Applicant urges that Thomas Jr. et al do not mention polysaccharide components. Applicant urges that there is no requirement or suggestion that the antigen be a polysaccharide. Applicant urges that all of the exemplified antigens in Thomas Jr. et al are proteins or peptides. Applicant urges that Thomas Jr. et al do not anticipate the claimed invention nor does Thomas Jr. et al suggest the claimed invention. Applicant urges that Thomas Jr. et al do not teach the use of rARU as a carrier. Applicant urges that Thomas Jr. et al teach that the rARU is utilized as an antigen. Applicant urges that Thomas Jr. et al does not teach each and every element of the claimed invention.

Applicant's arguments filed October 21, 2002 have been fully considered but they are not persuasive. It is the Examiner's position that there is nothing of the record to show why the immunogenic composition of the reference is not the same as the claimed

immunogenic composition. Applicant appears to argue limitations that are not in the claims with their assertion that Thomas Jr. et al do not use of rARU as a carrier instead they the rARU as an antigen. The claims are drawn to an immunogenic composition for eliciting an immune response to a pathogenic organism which composition comprises a recombinant protein and a polysaccharide component, wherein said protein comprises the toxin A repeating units (rARU) of *Clostridium difficile* and said polysaccharide component is characteristic of pathogenic microorganism, which pathogenic microorganism is other than *C. difficile*. Thomas Jr. et al teach compositions that contain an antigen, a toxin (*Clostridium difficile, C. novyi, C. sordellii, C. perfringens, C. tetani and C. botulinum*) or a fragment or derivative thereof having adjuvant activity in a pharmaceutically acceptable vehicle (i.e. water, a saline solution, phosphate-buffered saline, a bicarbonate solution or a form of a suppository) (column 3). Thomas Jr. et al teach that fusion proteins (i.e. C. difficile toxin A or B fused to an antigen) may be included in this invention (column 2). Thomas Jr. et al teach that <u>any</u> antigen to which a protective and/or therapeutic immune response is desired may be administered with an adjuvant of this invention, which include *Escherichia coli*, *Shigella* and *Neisseria gonorrhoeae* which contain polysaccharide antigens (columns 2-3). Therefore, there is no reason why the immunogenic composition of Thomas Jr. et al does not anticipate the claimed invention.

5. The rejection of claims 1, 3, 6, 13-15, 19-20, 23-24, 36-39 and 63 under 35 U.S.C. 103 (a) as unpatentable over Thomas Jr. et al in view of Schneerson et al is maintained for the reasons set forth on pages 7-9, paragraph 7 of the previous Office Action.

The rejection was on the grounds that Thomas, Jr. et al disclose a composition that contains an antigen, a toxin (*Clostridum difficile, C. novyi, C. sordellii, C. perfringens, C. tetani and C. botulinum*) or a fragment or derivative thereof having adjuvant activity in a pharmaceutically acceptable vehicle (i.e. water, a saline solution, phosphate-buffered saline, a bicarbonate solution or a form of a suppository). Thomas, Jr. et al disclose that toxins included in the composition included *C. difficile* toxin A, *C. Difficile* toxin B, both *C. difficile* toxins A and B, or a fragment or derivative thereof. Thomas, Jr. et al disclose that the *C. difficile* toxins contain the repeats which make up the carbohydrate binding domain of toxin A (ARU) or derivatives thereof. Thomas, Jr. et al disclose that the toxins may be recombinant, synthetic or part of a fusion protein which includes a *Helicobactor pylori* urease or polypeptide which facilitates purification of the fusion protein covalently conjugated to an antigen, chemically cross-linked to an antigen or toxoided (i.e. rendered less toxic) (column 3). Thomas, Jr. et al disclose that intranasal administration of antigens give rise to mucosal immune responses in the upper respiratory tract, gastrointestinal and genito-urinary tracts (column 4). Thomas Jr. et al teach that any antigen to which a protective and/or therapeutic immune response is desired may be administered with the adjuvant of the invention (column 2, lines 57-59). Thomas Jr. et al teach the use of C. difficile toxin A and ovalbumin used as a vaccine (column 13, Example V). Thomas Jr. et al teach that the invention may be used to treat patients including but not limited to mammals such as humans, cows, horses, pigs, dogs, cats, sheep and goats (column 3, lines 16-19).

Thomas, Jr. et al do not teach serotype 14 *Streptococcus pneumoniae*.

Schneerson et al teach a conjugate vaccine composed of serotype 14 *Streptococcus pneumoniae* capsular polysaccharide bound to Pertussis Toxin. Schneerson et al teach that serotype 14 *Streptococcus pneumoniae* is one of the common types isolated from patients of all ages with infections caused by *Streptococcus pneumoniae*. Schneerson et al teach that serotype 14 *Streptococcus pneumoniae* capsular polysaccharide does not elicit protective levels of antibodies in infants and children and is a less than optimal immunogen of the 23-valent vaccine for adults. Schneerson et al teach that Pertussis toxin is both a virulence factor and protective antigen of *Bordetella pertussis*. Schneerson et al devised a synthetic scheme to prepare a conjugate of serotype 14 *Streptococcus pneumoniae* and Pertussis toxin. Schneerson et al further teach that the serotype 14 *Streptococcus pneumoniae*-Pertussis toxin conjugate elicited antibodies in mice to serotype 14 *Streptococcus pneumoniae* at levels estimated to be protective in humans and elicited neutralizing antibodies to Pertussis toxin (see the Abstract).

It would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add the serotype 14 *Streptococcus pneumoniae* capsular polysaccharides of Schneerson et al to the immunogenic composition as taught by Thomas, Jr. et al because Schneerson et al teach that 14 *Streptococcus pneumoniae* capsular polysaccharide is a poor immunogen in humans when administered alone, but conjugating these capsular polysaccharides to proteins enhances their immunogenicity (the entire article). It would be expected barring evidence to the contrary that the addition of serotype 14 *Streptococcus pneumoniae* capsular polysaccharides to *Clostridium* toxin would provide a protective and/or therapeutic response.

Applicant urges that Thomas Jr. et al disclose *C. difficile* adjuvants in the context only of vaccines, which are designed for administration to the mucosa. Applicant urges that Examples 1 and 2 describe experiments of Thomas Jr. et al where vaccines are administered intranasally. Applicant urges that Examples 3 and 4 of Thomas Jr. et al describe the use of toxin A fusion protein wherein the repeating unit is coupled to GST is not used as an adjuvant but as the antigen to which response is elicited. Applicant urges that Example 5 uses toxin A as the illustrative adjuvant and describes vaginal and rectal administration. Applicant urges that there is no specific description of injecting compositions where a *C. difficile* derived protein is an adjuvant in Thomas Jr. et al. Applicant urges that the vaccines described in Thomas Jr. et al are not formulated for injection as required by the claims. Applicant urges that all secondary references describe administration by injection. Applicant urges that Thomas Jr. et al fail to teach or suggest and teach away from compositions that are formulated for injection. Thomas et al fail to identify rARU as an adjuvant. Applicant urges that polysaccharides represent a species of the genus of antigens and rARU represents a species of C. *difficile* toxins. Applicant urges that there is no mention of these species in the appropriate context of Thomas Jr. et al. Applicant urges that the failure of Thomas Jr. et al to suggest these

limitations is not remedied by any of the secondary references. Applicant urges that Thomas Jr. et al do not teach *S. pneumoniae*. Applicant urges that there appears to be no suggestion to combine Schneerson et al with Thomas Jr. et al in view of the focus of Thomas Jr. et al on only protein antigens and Thomas Jr. et al is directed to mucosal administration while Schneerson et al is directed to injection. Applicant urges that there is no incentive to combine these documents, even if they are combined the invention is not suggested as the limitation to rARU as a carrier is not suggested by either of the documents alone or in combination.

Applicant's arguments filed October 21, 2002 have been fully considered but they are not persuasive. It is the Examiner's position that applicant argues the references individually without clearly addressing the combination of teachings. It is the combination of all of the cited and relied upon references which make up the state of the art with respect to the claimed invention. The claims are drawn to an immunogenic composition for eliciting an immune response to a pathogenic organism which composition comprises a recombinant protein and a polysaccharide component, wherein said protein comprises the toxin A repeating units (rARU) of *Clostridium difficile* and said polysaccharide component is characteristic of pathogenic microorganism, which pathogenic microorganism is other than *C. difficile*. Thomas Jr. et al teach compositions that contain an antigen, a toxin or a fragment or derivative thereof having adjuvant activity in a pharmaceutically acceptable vehicle (column 3). Thomas Jr. et al teach that fusion proteins (i.e. C. difficile toxin A or B fused to an antigen) may be included in this invention (column 2). Thomas Jr. et al teach that any antigen to which a

protective and/or therapeutic immune response is desired may be administered with an adjuvant of this invention, the antigens include *Escherichia coli*, *Shigella* and *Neisseria gonorrhoeae* which contain polysaccharide antigens (columns 2-3). Thomas, Jr. et al do not teach serotype 14 *Streptococcus pneumoniae*. However, Schneerson et al teach a conjugate vaccine composed of serotype 14 *Streptococcus pneumoniae* capsular polysaccharide bound to Pertussis Toxin. Therefore, it would have been obvious to couple the *C. difficile* toxin A as taught by Thomas Jr. et al to the serotype 14 *Streptococcus pneumoniae* (i.e. antigen) of Schneerson et al because Thomas Jr. et al teach that any antigen to which a protective and/or therapeutic immune response is desired may be administered with an adjuvant of this invention. Although Examples 1-2 teach intranasal administration and Example 5 of Thomas Jr. et al teach rectal and vaginal administration, Thomas Jr. et al teach that the compositions of the invention may also be administered by parenteral, intravenous, subcutaneous, intraperitoneal or intramuscular routes (column 3). Therefore, the compositions of Thomas Jr. et al are formulated for injection. Examples 3 and 4 of Thomas Jr. et al teach that the adjuvant activity of GST-ARU was tested by intranasal immunization of GST-ARU and/or Toxin A with ovalbumin and all immune responses analyzed were significantly enhanced when GST-ARU was used as an adjuvant (column 13). Therefore, Thomas Jr. et al teach the use of ARU as an adjuvant. Applicant appears to argue limitations that are not in the claims. There is nothing on the record to show that the combination of teachings would not suggest the claimed invention.

6. The rejection of claims 1, 3, 6, 13-15, 19-20, 25-26, 36-39 and 63 under 35 U.S.C. 103 (a) as unpatentable over Thomas Jr. et al in view of Taylor et al is maintained for the reasons set forth on pages 9-11, paragraph 8 of the previous Office Action.

The rejection was on the grounds that Thomas, Jr. et al disclose a composition that contains an antigen, a toxin (*Clostridum difficile, C. novyi, C. sordellii, C. perfringens, C. tetani and C. botulinum*) or a fragment or derivative thereof having adjuvant activity in a pharmaceutically acceptable vehicle (i.e. water, a saline solution, phosphate-buffered saline, a bicarbonate solution or a form of a suppository). Thomas, Jr. et al disclose that toxins included in the composition included *C. difficile* toxin A, *C. Difficile* toxin B, both *C. difficile* toxins A and B, or a fragment or derivative thereof. Thomas, Jr. et al disclose that the *C. difficile* toxins contain the repeats which make up the carbohydrate binding domain of toxin A (ARU) or derivatives thereof. Thomas, Jr. et al disclose that the toxins may be recombinant, synthetic or part of a fusion protein which includes a *Helicobactor pylori* urease or polypeptide which facilitates purification of the fusion protein covalently conjugated to an antigen, chemically cross-linked to an antigen or toxoided (i.e. rendered less toxic) (column 3). Thomas, Jr. et al disclose that intranasal administration of antigens give rise to mucosal immune responses in the upper respiratory tract, gastrointestinal and genito-urinary tracts (column 4). Thomas Jr. et al teach that any antigen to which a protective and/or therapeutic immune response is desired may be administered with the adjuvant of the invention (column 2, lines 57-59). Thomas Jr. et al teach the use of C. difficile toxin A and ovalbumin used as a vaccine (column 13, Example V). Thomas Jr. et al teach that the invention may be used to treat patients including but not limited to mammals such as humans, cows, horses, pigs, dogs, cats, sheep and goats (column 3, lines 16-19).

Thomas Jr. et al do not teach *Shigella flexneri* Type 2a.

Taylor et al teach a conjugate vaccine comprising *Shigella dysenteria* type 1, *Shigella flexneri* type 2a and *Shigella sonnei* bound to bacterial toxoids (carrier proteins). Taylor et al teach that *Shigella dysenteria* type 1, *Shigella flexneri* type 2a and *Shigella sonnei* administered to mice alone are not immunogenic. Taylor et al further teach that *Shigella dysenteria* type 1, *Shigella flexneri* type 2a and *Shigella sonnei* conjugated to a carrier protein injected into mice subcutaneously in saline solutions elicited serum IgG and IgM antibodies with booster responses. When the *Shigella dysenteria* type 1, *Shigella flexneri* type 2a and *Shigella sonnei* conjugate were adsorbed with alum further enhancement of their immunogenicity was observed (see the Abstract).

It would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add the *Shigella flexneri* 2a capsular polysaccharides of Taylor et al to the immunogenic composition as taught by Thomas Jr. et al because Taylor et al teach that *Shigella flexneri* 2a capsular polysaccharides are poor immunogens when

administered alone, but conjugating these capsular polysaccharides to proteins enhances their immunogenicity (the entire article). It would be expected barring evidence to the contrary that the addition of the *Shigella flexneri* 2a capsular polysaccharides to *Clostridium* toxin would provide a protective and/or therapeutic response.

Applicant urges that all secondary references describe administration by injection. Applicant urges that Thomas Jr. et al fail to teach or suggest and teach away from compositions that are formulated for injection. Thomas et al fail to identify rARU as an adjuvant. Applicant urges that polysaccharides represent a species of the genus antigens and rARU represents a species of the genus *C. difficile* toxins and there is no mention of these species in the appropriate context of Thomas Jr. et al. Applicant urges that the failure of Thomas Jr. et al suggest these limitations is not remedied by any of the secondary references. Applicant urges that Thomas Jr. et al do not teach *Shigella*. Applicant urges that Taylor et al describes polysaccharide conjugates of *Shigella* polysaccharides to bacterial toxoids. Applicant urges that Thomas Jr. et al suggest only enhancing the immune response of protein or peptide antigens rather than polysaccharides and Thomas Jr. et al teach compositions that are directed to mucosal administration while the compositions of Schneerson et al are directed to injection. Applicant urges that there is no motivation to combine these documents. Applicant urges even if Thomas Jr. et al is combined with Schneerson et al, the invention is not suggested as the limitation to rARU as a carrier is not suggested by either of the documents alone or in combination.

Applicant's arguments filed October 21, 2002 have been fully considered but they are not persuasive. It is the Examiner's position that applicant argues the references

individually without clearly addressing the combination of teachings. It is the combination of all of the cited and relied upon references which make up the state of the art with respect to the claimed invention. The claims are drawn to an immunogenic composition for eliciting an immune response to a pathogenic organism which composition comprises a recombinant protein and a polysaccharide component, wherein said protein comprises the toxin A repeating units (rARU) of *Clostridium difficile* and said polysaccharide component is characteristic of pathogenic microorganism, which pathogenic microorganism is other than *C. difficile*. Thomas Jr. et al teach compositions that contain an antigen, a toxin or a fragment or derivative thereof having adjuvant activity in a pharmaceutically acceptable vehicle (column 3). Thomas Jr. et al teach that fusion proteins (i.e. *C. difficile* toxin A or B fused to an antigen) may be included in this invention (column 2). Thomas Jr. et al teach that any antigen to which a protective and/or therapeutic immune response is desired may be administered with an adjuvant of this invention, the antigens include *Escherichia coli*, *Shigella* and *Neisseria gonorrhoeae* which contain polysaccharide antigens (columns 2-3). Thomas Jr. et al do not specifically teach *Shigella flexneri* type 2a. However, Taylor et al teach a conjugate vaccine comprising *Shigella dysenteria* type 1, *Shigella flexneri* type 2a and *Shigella sonnei* bound to bacterial toxoids (carrier proteins). Therefore, it would have been obvious to couple the *C. difficile* toxin A as taught by Thomas Jr. et al to the *Shigella flexneri* type 2a (i.e. antigen) of Taylor et al because Thomas Jr. et al teach that any antigen to which a protective and/or therapeutic immune response is desired may be administered with an adjuvant of this invention. Thomas Jr. et al teach that the

compositions of the invention may also be administered by parenteral, intravenous, subcutaneous, intraperitoneal or intramuscular routes (column 3). The Examiner disagrees with the Applicant's assertion that Thomas Jr. et al do not teach ARU used as an adjuvant. Thomas Jr. et al teach that the adjuvant activity of GST-ARU was tested by intranasal immunization of GST-ARU and/or Toxin A with ovalbumin and all immune responses analyzed were significantly enhanced when GST-ARU was used as an adjuvant (column 13). Applicant appears to argue limitations that are not in the claims. There is nothing on the record to show that the combination of teachings would not suggest the claimed invention.

The arguments addressing the combined teachings of Thomas Jr. et al in view of Schneerson et al are addressed in paragraph 4 of this Office action.

7. The rejection of claims 1, 3, 6, 13-15, 19-20, 28-29, 36-39 and 63 under 35 U.S.C. 103 (a) as unpatentable over Thomas Jr. et al in view of Devi et al is maintained for the reasons set forth on pages 12-14, paragraph 9 of the previous Office Action.

The rejection was on the grounds that Thomas, Jr. et al disclose a composition that contains an antigen, a toxin (*Clostridum difficile, C. novyi, C. sordellii, C. perfringens, C. tetani and C. botulinum*) or a fragment or derivative thereof having adjuvant activity in a pharmaceutically acceptable vehicle (i.e. water, a saline solution, phosphate-buffered saline, a bicarbonate solution or a form of a suppository). Thomas, Jr. et al disclose that toxins included in the composition included *C. difficile* toxin A, *C. Difficile* toxin B, both *C. difficile* toxins A and B, or a fragment or derivative thereof. Thomas, Jr. et al disclose that the *C. difficile* toxins contain the repeats which make up the carbohydrate binding domain of toxin A (ARU) or derivatives thereof. Thomas, Jr. et al disclose that the toxins may be recombinant, synthetic or part of a fusion protein which includes a *Helicobactor pylori* urease or polypeptide which facilitates purification of the fusion protein covalently conjugated to an antigen, chemically cross-linked to an antigen or toxoided (i.e. rendered less toxic) (column 3). Thomas, Jr. et al disclose that intranasal administration of antigens give rise to mucosal immune responses in the

upper respiratory tract, gastrointestinal and genito-urinary tracts (column 4). Thomas Jr. et al teach that any antigen to which a protective and/or therapeutic immune response is desired may be administered with the adjuvant of the invention (column 2, lines 57-59). Thomas Jr. et al teach the use of C. difficile toxin A and ovalbumin used as a vaccine (column 13, Example V). Thomas Jr. et al teach that the invention may be used to treat patients including but not limited to mammals such as humans, cows, horses, pigs, dogs, cats, sheep and goats (column 3, lines 16-19).

Thomas Jr. et al do not teach *Escherichia coli* K1 or *Neisseria meningitides* serogroup B.

Devi et al teach that the capsular polysaccharides of *Escherichia coli* K1 and *Neisseria meningitidis* serogroup B are identical (poly{(2→8)-α-N-acetylneuaminic acid)} or poly(α2-8NeuNAc) and serve as essential virulence factors and protective antigens for both pathogens. Devi et al teach that attempts have been made to induce protective immunity to *Escherichia coli* K1 and *Neisseria meningitidis* serogroup B have been thwarted because poly(α2-8NeuNAc), alone or complexed to outer membrane proteins induced low transient levels of IgM antibodies (page 7175). Devi et al teach that when the capsular polysaccharides of *Escherichia coli* K1 and *Neisseria meningitidis* serogroup B are conjugated to tetanus toxin (a carrier protein) and injected into mice in a saline solution the capsular polysaccharides elicit both poly(α2-8NeuNAc) IgM and IgG antibodies. Devi et al further teach that re-injection elicited booster responses of both isotypes (T-dependent properties) at dosages applicable for clinical use (page 7178).

It would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add the capsular polysaccharides of *Escherichia coli* K1 and *Neisseria meningitidis* serogroup B as taught by Devi et al to the immunogenic composition as taught by Thomas Jr. et al because Devi et al teach that capsular polysaccharides are poor immunogens when administered alone, but conjugating these capsular polysaccharides to tetanus toxin (carrier proteins) enhances their immunogenicity (the entire article). It would be expected barring evidence to the contrary that the addition of capsular polysaccharides of *Escherichia coli* K1 and *Neisseria meningitidis* serogroup B to the *Clostridium* toxin would provide a protective and/or therapeutic response.

Applicant urges that Devi et al is directed to *Neisseria meningitidis* and *Escherichia coli*. Applicant urges that the secondary document is cited to show polysaccharide antigens from relevant organisms coupled to a different protein not *C. difficile*. Applicant urges that the combination is not suggested for similar reasons above. Applicant urges even if Thomas Jr. et al is combined with Schneerson et al, the

invention is not suggested as the limitation to rARU as a carrier is not suggested by either of the documents alone or in combination.

Applicant's arguments filed October 21, 2002 have been fully considered but they are not persuasive. It is the Examiner's position that applicant argues the references individually without clearly addressing the combination of teachings. It is the combination of all of the cited and relied upon references which make up the state of the art with respect to the claimed invention. The claims are drawn to an immunogenic composition for eliciting an immune response to a pathogenic organism which composition comprises a recombinant protein and a polysaccharide component, wherein said protein comprises the toxin A repeating units (rARU) of *Clostridium difficile* and said polysaccharide component is characteristic of pathogenic microorganism, which pathogenic microorganism is other than *C. difficile*. Thomas Jr. et al teach compositions that contain an antigen, a toxin or a fragment or derivative thereof having adjuvant activity in a pharmaceutically acceptable vehicle (column 3). Thomas Jr. et al teach that fusion proteins (i.e. *C. difficile* toxin A or B fused to an antigen) may be included in this invention (column 2). Thomas Jr. et al teach that any antigen to which a protective and/or therapeutic immune response is desired may be administered with an adjuvant of this invention, the antigens include *Escherichia coli*, *Shigella* and *Neisseria gonorrhoeae* which contain polysaccharide antigens (columns 2-3). Thomas Jr. et al do not specifically teach the capsular polysaccharides of *Escherichia coli* K1 and *Neisseria meningitidis* serogroup B. However, Devi et al teach that when the capsular polysaccharides of *Escherichia coli* K1 and *Neisseria meningitidis* serogroup B are

conjugated to tetanus toxin (a carrier protein) and injected into mice in a saline solution the capsular polysaccharides elicit both poly(α2-8NeuNAc) IgM and IgG antibodies. Therefore, it would have been obvious to couple the *C. difficile* toxin A as taught by Thomas Jr. et al to the capsular polysaccharides of *Escherichia coli* K1 and *Neisseria meningitidis* serogroup B (i.e. antigen) of Devi et al because Thomas Jr. et al teach that any antigen to which a protective and/or therapeutic immune response is desired may be administered with an adjuvant of this invention. Thomas Jr. et al teach that the compositions of the invention may also be administered by parenteral, intravenous, subcutaneous, intraperitoneal or intramuscular routes (column 3). The Examiner disagrees with the Applicant's assertion that Thomas Jr. et al do not teach ARU used as an adjuvant. Thomas Jr. et al teach that the adjuvant activity of GST-ARU was tested by intranasal immunization of GST- ARU and/or Toxin A with ovalbumin and all immune responses analyzed were significantly enhanced when GST-ARU was used as an adjuvant (column 13). Applicant appears to argue limitations that are not in the claims. There is nothing on the record to show that the combination of teachings would not suggest the claimed invention.

The arguments addressing the combined teachings of Thomas Jr. et al in view of Schneerson et al are addressed in paragraph 4 of this Office action.

8. The rejection of claims 1, 3, 6, 13-15, 19, 30-31, 33, 36-39 and 63 under 35 U.S.C. 103 (a) as unpatentable over Thomas Jr. et al in view of Fattom et al is

maintained for the reasons set forth on pages 14-17, paragraph 10 of the previous Office Action.

The rejection was on the grounds that Thomas, Jr. et al disclose a composition that contains an antigen, a toxin (*Clostridum difficile, C. novyi, C. sordellii, C. perfringens, C. tetani and C. botulinum*) or a fragment or derivative thereof having adjuvant activity in a pharmaceutically acceptable vehicle (i.e. water, a saline solution, phosphate-buffered saline, a bicarbonate solution or a form of a suppository). Thomas, Jr. et al disclose that toxins included in the composition included *C. difficile* toxin A, *C. Difficile* toxin B, both *C. difficile* toxins A and B, or a fragment or derivative thereof. Thomas, Jr. et al disclose that the *C. difficile* toxins contain the repeats which make up the carbohydrate binding domain of toxin A (ARU) or derivatives thereof. Thomas, Jr. et al disclose that the toxins may be recombinant, synthetic or part of a fusion protein which includes a *Helicobactor pylori* urease or polypeptide which facilitates purification of the fusion protein covalently conjugated to an antigen, chemically cross-linked to an antigen or toxoided (i.e. rendered less toxic) (column 3). Thomas, Jr. et al disclose that intranasal administration of antigens give rise to mucosal immune responses in the upper respiratory tract, gastrointestinal and genito-urinary tracts (column 4). Thomas Jr. et al teach that any antigen to which a protective and/or therapeutic immune response is desired may be administered with the adjuvant of the invention (column 2, lines 57-59). Thomas Jr. et al teach the use of C. difficile toxin A and ovalbumin used as a vaccine (column 13, Example V). Thomas Jr. et al teach that the invention may be used to treat patients including but not limited to mammals such as humans, cows, horses, pigs, dogs, cats, sheep and goats (column 3, lines 16-19).

Thomas Jr. et al do not teach *Staphylococcus aureus* type 5 or Type 8 capsular polysaccharides or *Pseudomonas aerginosa*.

Fattom et al teach vaccines composed of *Staphylococcus aureus* type 5 and Type 8 capsular polysaccharides conjugated to *Pseudomonas aerginosa* Exotoxin A. Fattom et al teach that *Staphylococcus aureus* type 5 and type 8 capsular polysaccharides are virulence factors and protective antigens for bacteremia caused by *Staphylococcus aureus*. Fattom et al teach that *Staphylococcus aureus* type 5 and type 8 capsular polysaccharides when injected into mice alone do not elicit a serum antibody response. Fattom et al teach that when *Staphylococcus aureus* type 5 and type 8 capsular polysaccharides are bound to a protein (i.e. *Pseudomonas aerginosa* exotoxin A) to form a conjugate both *Staphylococcus aureus* type 5 and type 8 elicit antibody responses. Fattom et al teach that *Staphylococcus aureus* type 5 and type 8 capsular polysaccharides acquire T-cell dependent properties as shown by their ability to respond to carrier priming and thus stimulate booster responses (see the Abstract).

It would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add the *Staphylococcus aureus* type 5 and type 8 capsular polysaccharides of Fattom et al to the immunogenic composition as taught by Thomas Jr. et al because Fattom et al teach that *Staphylococcus aureus* type 5 and type 8 capsular polysaccharides are poor immunogens in humans when administered alone,

but conjugating these capsular polysaccharides to proteins enhances their immunogenicity both for active immunization and for preparing high-titered antisera in volunteers for passive immunization (page 2368). It would be expected barring evidence to the contrary that the addition of *Staphylococcus aureus* type 5 and type 8 capsular polysaccharides to the *Clostridium* toxin would provide a protective and/or therapeutic response.

Applicant urges that the secondary document describes capsular polysaccharides from *S. aureus* which is included in the claims. Applicant urges that the combination is not suggested for the same reasons as set forth above. Applicant urges even if Thomas Jr. et al is combined with Schneerson et al, the invention is not suggested as the limitation to rARU as a carrier is not suggested by either of the documents alone or in combination. Applicant urges that in all cases the required combination of documents is taught away from Thomas Jr. et al and that Thomas Jr. et al is directed solely to peptide or protein antigens and focus on mucosal administration. Applicant urges that the secondary documents describe polysaccharide antigens coupled to other proteins there is no suggestion that rARU be substituted for the carrier described in the secondary documents. Thomas et al does not suggest rARU either, even the combination does not suggest the invention as claimed.

Applicant's arguments filed October 21, 2002 have been fully considered but they are not persuasive. It is the Examiner's position that applicant argues the references individually without clearly addressing the combination of teachings. It is the combination of all of the cited and relied upon references which make up the state of the art with respect to the claimed invention. The claims are drawn to an immunogenic composition for eliciting an immune response to a pathogenic organism which composition comprises a recombinant protein and a polysaccharide component,

wherein said protein comprises the toxin A repeating units (rARU) of *Clostridium difficile* and said polysaccharide component is characteristic of pathogenic microorganism, which pathogenic microorganism is other than *C. difficile*. Thomas Jr. et al teach compositions that contain an antigen, a toxin or a fragment or derivative thereof having adjuvant activity in a pharmaceutically acceptable vehicle (column 3). Thomas Jr. et al teach that fusion proteins (i.e. C. difficile toxin A or B fused to an antigen) may be included in this invention (column 2). Thomas Jr. et al teach that any antigen to which a protective and/or therapeutic immune response is desired may be administered with an adjuvant of this invention, the antigens include *Escherichia coli*, *Shigella* and *Neisseria gonorrhoeae* which contain polysaccharide antigens (columns 2-3). Thomas Jr. et al do not teach *Staphylococcus aureus* type 5 or Type 8 capsular polysaccharides or *Pseudomonas aerginosa*. Fattom et al teach vaccines composed of *Staphylococcus aureus* type 5 and Type 8 capsular polysaccharides conjugated to *Pseudomonas aerginosa* Exotoxin A. Therefore, it would have been obvious to couple the *C. difficile* toxin A as taught by Thomas Jr. et al to the *Staphylococcus aureus* type 5 or Type 8 capsular polysaccharides or *Pseudomonas aerginosa* (i.e. antigen) of Fattom et al because Thomas Jr. et al teach that any antigen to which a protective and/or therapeutic immune response is desired may be administered with an adjuvant of this invention. However, Thomas Jr. et al teach that the compositions of the invention may also be administered by parenteral, intravenous, subcutaneous, intraperitoneal or intramuscular routes (column 3). Applicant appears to argue limitations that are not in

the claims. There is nothing on the record to show that the combination of teachings would not suggest the claimed invention.

The arguments addressing the combined teachings of Thomas Jr. et al in view of Schneerson et al are addressed in paragraph 4 of this Office action.

9. No claims allowed.

10. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
November 16, 2002

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